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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,506	01/05/2005	Heinz Von Der Kammer	P67785US1	6896

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,506	VON DER KAMMER ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,16-21,23 and 24* is/are pending in the application.

4a) Of the above claim(s) *1-13,16-21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 12, 2008 has been entered.

Claims 1-13 and 16-21, 23, and 24 are pending. Claims 14, 15, and 22 are cancelled. Claim 24 is newly added. Claims 1-13 and 16-21, and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claim 24 is currently under examination.

This application 10/510,506 filed on Jan. 05, 2005 is a 371 of PCT/EP03/03626 filed on 04/08/2003 claims benefit of the provisional application 60/370,214 filed on 04/08/2002.

Claim Objection

2. Claim 24 is objected to because of the following informalities: Claim 24 line 2 recites the limitation "said modulator is modulating substances ---", which is an improper verb tense, and it should read "modulates";

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear whether the claimed method is intended to be a screen for a modulator of Alzheimer's (line 3 of step (d) of claim 24) or a modulator of ADPRTL (line 1 of claim 24).

Step (b) recites measuring the substance**s,** yet the preamble seems to narrow it to one substance in reciting "the minor vault protein ADPTRL1 as shown in SEQ ID NO: 2". It is unclear whether "the minor vault protein ADPTRL1 as shown in SEQ ID NO: 2" is the only modulating substance or not. As a related issue, line 2-3 of the claim recites "**a** translation product of **a** gene coding for **a** vault protein, **the** minor vault protein as shown in...". It is not clear whether multiple translation products and/or multiple minor vault proteins are recited in the claim.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

4. The previous rejection of claim 22 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is **maintained** as it relates to newly added claim 24. The rejection is moot with respect to claim 22 as claim 22 has been cancelled.

For clarity of this office action, Applicant's remark, lines 8-16, page 13, filed on 03/12/2008 on the newly added claim 24 is cited as follows:

"Present replacement claim 24 does not recite "(ii) derivatives thereof," the subject matter---- of rejected claim 22 --- allegedly lacking written descriptive support. Since the subject matter allegedly lacking written descriptive support is no longer present in any active claim, the reason for the rejection is rendered moot. Accordingly, applicants submit that the rejection under §112, ¶1, for allegedly failing to comply with the requirement for a written description, is overcome and withdrawal of the rejection appears to be in order."

Accordingly, newly added claim 24 is directed to an assay for screening for a modulator of the minor vault protein ADPRTL1, whereby said modulator is a modulating substance consisting of *a* translation product of *a* gene coding for *a* vault protein, the minor vault protein ADPRTL1 *as shown in* SEQ ID NO: 2.

With regard to the phrase "*a* translation product of *a* gene coding for *a* vault protein, the minor vault protein ADPRTL1 *as shown in* SEQ ID NO: 2", the phrase continues to encompasses any fragment, or derivative, or variant of a translation product of a gene coding for the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2. Furthermore, "*a* gene" encompasses multiple genes. In this regard, the specification indicates that the "Proteins and polypeptides" of the instant invention include variants, fragments and chemical derivatives of the protein comprising the amino acid sequence of SEQ ID NO. 2. As indicated in the specification, they can include proteins and polypeptides, which can be isolated from nature or be produced by

recombinant and/or synthetic means. Native proteins or polypeptides refer to naturally occurring truncated or secreted forms, naturally occurring variant forms (e.g. splice-variants) and naturally occurring allelic variants (See paragraph [0054], right column, page 3, US 2006/0073480). Relevant to the claimed invention, the specification further discloses that the instant invention further features a protein molecule shown in SEQ ID NO. 2, said protein molecule being a translation product of the gene coding for a vault protein, in particular the minor vault protein ADPRTL1, or a fragment, or derivative, or variant thereof, for use as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease (See paragraph [0055], page 8, US 2006/0073480).

With regard to the connection between ADPRTL1 as set forth in SEQ ID No: 2 and Alzheimer's disease (AD), the specification discloses that the identification of the differential expression of the human gene coding for minor vault protein ADPRTL1 by a fluorescence differential display screen. The differential expression reflects an *up-regulation of human minor vault protein ADPRTL1 gene transcription* in the temporal cortex compared to the frontal cortex of AD patients (See paragraph [0061], right column, page 9, US 2006/0073480).

It is noted that claim 24 as written would read on any variation (including functionally homologous vault proteins) and/or fragment of the human minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2. However, the translation products of the genes coding for derivatives of the minor vault protein ADPRTL1 as shown in SEQ ID NO: 2 encompassed within the genus of a gene coding for a vault protein, the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2, have not been disclosed. Based upon the prior art there is expected to be variation among the species of genes coding for vault proteins, because the sequence of the genes involved in coding

for a vault protein would be expected to vary among individuals. The specification discloses amino acid sequences of human minor vault protein ADPRTL1 as SEQ ID NO: 2 (full length being 1724 amino acid residues). There is no evidence on the record of a relationship between the structure of any vault protein sequences and derivatives thereof, and the claimed SEQ ID NO: 2 sequences for other genes encoding vault proteins that would provide any reliable information about the structure of other vault proteins, variants, and fragments thereof, within the genus. There is no evidence on the record that the asserted human minor vault protein ADPRTL1 sequences had a known structural relationship to any other vault protein sequences; the specification discloses only human minor vault protein ADPRTL1 as SEQ ID NO: 2 obtained from an undisclosed origin; the art indicated that there is variation between minor vault protein ADPRTL1 (as well as between other vault proteins) and their functions. The specification did disclose the nucleic acid sequences of the gene encoding the human minor vault protein ADPRTL1 as set forth in SEQ ID No: 2, the claimed human minor vault protein ADPRTL1, neither did the specification disclose any information regarding the functions of human minor vault protein ADPRTL1 relevant to modulation of Alzheimer's disease, as recited in step (d) of claim 24.

There is no evidence of record that would indicate that any of the claimed variants and fragments of human minor vault protein ADPRTL1 disclosed in SEQ ID No: 2 that share high homology to human minor vault protein ADPRTL1 disclosed in SEQ ID No: 2 even have the biological activity of a minor vault protein ADPRTL1. In the absence of *a functional assay* it would not be possible to test variants of the claimed sequences for biological activity. Also with regard to the claimed allelic variants, the skilled artisan cannot envision the structure of such a

variant because such variants are randomly produced in nature, and cannot be predicted from a known sequence. The specification does not teach any characteristics of an "allelic" variant that would distinguish it from a non-natural variant constructed by the hand of man. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because the human minor vault protein ADPRTL1 disclosed in SEQ ID No: 2 is not representative of the claimed genus. Consequently, since Applicant was in possession of only the human minor vault protein ADPRTL1 disclosed in SEQ ID No: 2 and since the art recognized variation among the species of the genus of a vault protein, variants, and fragments thereof, the human minor vault protein ADPRTL1 disclosed in SEQ ID No: 2 was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of the genus of a vault protein, variants, and fragments thereof as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Scope of Enablement

5. Previous scope of enablement rejection of claim 22 under 35 U.S.C. 112, first paragraph is **moot** because the claim has been cancelled.

However, newly added claim 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an assay for screening for a modulator of the minor

vault protein ADPRTL1 as set forth SEQ ID NO: 2, the method comprising: a) contacting a cell with a test compound; b) measuring the activity and/or level of ADPTRL1; c) measuring the activity and/or level of ADPRTL1 in a control cell not contacted with the test compound; and d) comparing the levels and/or activities of ADPRTL1 in the cells of steps b) and c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of the minor vault protein ADPRTL1 as set forth SEQ ID NO: 2, **does not** reasonably provide enablement for (1) any fragment of translation product of any gene coding the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2, or (2) the said assay for screening for any modulator of Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. *This rejection is necessitated by claim amendments filed by Applicant on 03/12/2007, which added new claim 24.*

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the instant invention is directed to an assay for screening for a modulator of the minor vault protein ADPRTL1, whereby the modulator is modulating the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2. However, Applicant fails to provide a necessary nexus between "a modulator of the minor vault protein ADPRTL1" and "a modulator of Alzheimer's disease". The specification merely provides that the mRNA levels of ADPRTL1 in the cells from patients with Alzheimer's disease are up-regulated compared to control healthy subject.

The breadth of the claim encompasses an assay for screening for a modulator of the minor vault protein ADPRTL1, whereby said modulator is modulating *any* fragment of translation product of any gene coding the minor vault protein ADPRTL1 as shown in SEQ ID NO: 2, and the said assay for screening for *any* modulator of Alzheimer's disease.

The specification discloses that the identification of the differential expression of the human gene coding for minor vault protein ADPRTL1 by a fluorescence differential display screen. The differential expression reflects an *up-regulation of human minor vault protein ADPRTL1 gene transcription* in the temporal cortex compared to the frontal cortex of AD patients (See paragraph [0061], right column, page 9, US 2006/0073480). This is the only relevant connection between ADPRTL1 as shown in SEQ ID No: 2 and Alzheimer's disease (AD) disclosed in the specification. It is emphasized that, no guidance, prophetic or otherwise, is provided demonstrating that modulation of ADPRTL1 as shown in SEQ ID No: 2 would result in the treatment of modulation of Alzheimer's disease. Similarly, no working examples are

provided at all, prophetic or otherwise, demonstrating the effectiveness of the claimed assay for screening a modulator of Alzheimer's disease. That a gene is up-regulated in a disease is not evidence that modulating said gene, either up or down-regulating, will cause, prevent, treat or cure the disease.

The art also recognizes that Alzheimer's disease is characterized pathologically by a multitude of anatomical abnormalities such as the presence of amyloid plaques, neuron fibrillary tangles, changes in permeability of the blood brain barrier leading to vascular damage, as well as neuro-inflammation and neuro-degeneration. See for example **Small et al.** (Small et al., Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease, *Proc Natl Acad Sci U S A.* 97(11): 6037-42, 2000). Applicant fails to provide guidance on the treatment or modulation of these other features associated with Alzheimer's disease pathology, which would be encompassed by providing therapy (encompassed by the claim limitation "the test compound is a modulator of Alzheimer's disease" as recited in step (d) of claim 24 of instant application) to a patient having AD. Thus, while reducing the expression of ADPRTL1, using the claimed modulating substance identified by the claimed assay for screening modulator of ADPRTL1, would be temporarily reverse the molecular phenotype of Alzheimer's disease, it would not be expected to necessarily provide long-lasting therapeutic results because *up-regulation of ADPRTL1 is not the cause of Alzheimer's disease, rather the up-regulation of ADPRTL1 is an effect of Alzheimer's disease*. Additionally it is noted that both at the time of filing and now, effective therapy for Alzheimer's has eluded researchers despite knowledge and characterization of a number of proteins that are increased and associated with Alzheimer's

pathology. **De Lustig et al.** (De Lustig et al., Peripheral markers and diagnostic criteria in Alzheimer's disease: critical evaluations, *Rev Neurosci.* 5(3): 213-25, 1994) report that there are still no effective therapies for the pathology and the disease thus follows an inevitable degenerative course. And a more recent review by **Vickers** (Vickers, A vaccine against Alzheimer's disease: developments to date. *Drugs Aging.* 19(7): 487-94, 2002) notes that there is no effective treatment currently available to reverse, slow down or prevent the course of Alzheimer's disease and most other brain diseases and conditions. Thus, the art recognizes unpredictability in the ability to effectively treat neurodegenerative diseases, and Alzheimer's disease in particular. It is, therefore, unpredictable; given the lack of guidance in the specification that modulation of ADPRTL1 would treat or modulate Alzheimer's in any way.

With regard to the phrase "*a* translation product of *a* gene coding for *a* vault protein, the minor vault protein ADPRTL1 *as shown in* SEQ ID NO: 2", as discussed in the preceding rejection of claim 24 under 35 U.S.C. 112, first paragraph, written description, the phrase continues to encompass any fragment, or derivative, or variant of a translation product of a gene coding for the minor vault protein ADPRTL1 as shown in SEQ ID NO: 2. As indicated in the specification, ADPRTL1 and derivatives thereof can include proteins and polypeptides, which can be isolated from nature or be produced by recombinant and/or synthetic means. The specification further discloses that the instant invention further features a protein molecule shown in SEQ ID NO. 2, said protein molecule being a translation product of the gene coding for a vault protein, in particular the minor vault protein ADPRTL1, or a fragment, or derivative, or variant thereof, for use as *a screening target* for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease (See paragraph

[0055], page 8, US 2006/0073480). However, it is noted that the specification does not teach any characteristics of an "allelic" variant and/or a derivative of the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2, that is functional, especially in the context of modulation of Alzheimer's disease, and can be used as a target for an assay for screening for a modulator of any fragment or variant of the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2. A skilled person in the art will have to conduct experimentation to identify necessary and sufficient fragment(s) required for the function of the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2 (SEQ ID No: 2 being 1724 amino acid residues total) to make and use of the claimed assay using any fragment or variant of the minor vault protein ADPRTL1 as set forth in SEQ ID NO: 2 as the target of claimed assay for screening. This level of experimentation is not considered as routine, but is considered as undue. Therefore, in view of the breadth of the claims encompassing treatment or modulation of Alzheimer's disease, the lack of adequate guidance, data, evidence or working examples supporting a therapeutic effect of the claimed assay for screen, the unpredictability in the art of treatment of Alzheimer's disease in particular, and the complex nature of modulation of Alzheimer's disease encompassed by the claim of instant invention, one of skill in the art would find that undue experimentation would be required to practice the claimed invention.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. The previous rejection of claim 22 under 35 U.S.C. 102(b) as being anticipated by Rome et al., (Rome et al., PCT/US98/11348, WO 99/62547, listed in the IDS filed by the applicants) as evidenced by Lam et al., 2001 (Lam et al., beta-Amyloid efflux mediated by p-glycoprotein. *J Neurochem.* 76(4): 1121-8, 2001), is **maintained** as it relates to newly added claim 24. The rejection is moot with respect to claim 22 as claim 22 has been cancelled.

The Examiner notes that newly added claim 24 no longer recites "Alzheimer's disease, or related diseases or disorders". Rome et al. teach purified human minor vault protein p193 or purified biologically active variants thereof, or a combination of purified human minor vault protein p193 and biologically active variants thereof are disclosed, and a polynucleotide molecule encoding human minor vault protein p193, or the complementary DNA is also disclosed (See SEQ ID NO: 1 for DNA sequence and SEQ ID NO: 2 for p193/ADPTRL1 polypeptide sequences with 1724 amino acid residues). Rome et al. teach a method of diagnosing and a method of treating patients with multidrug resistant cancer. It is noted that "wherein ....indicates that the test compound is a modulator of Alzheimer's disease" is not an active step and the art meets all the active steps.

Conclusion

7. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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